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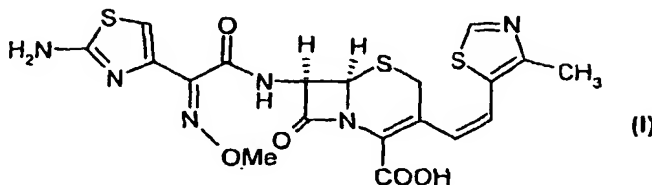
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(54) Title: A NEW PROCESS FOR THE PREPARATION OF CEFDITOREN USING THE THIOESTER OF THIAZOLYL-LACETIC ACID

formula (I)

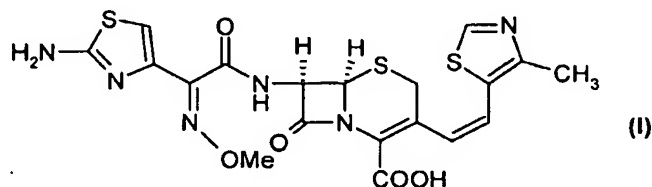


(57) Abstract: The present invention provides a process for the preparation of Cefditoren of formula (I) which comprises acylating 7-amino-cephem carboxylic acids of the general formula (IV), where R³ is hydrogen or trimethylsilyl with thioester derivatives of the formula (II), where R¹ represents C₁ - C₄ alkyl or phenyl in an organic solvent in the presence of an organic base at a temperature in the range of -10 °C to 30 °C.

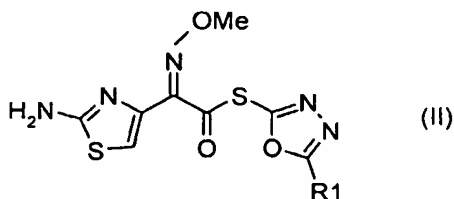
A NEW PROCESS FOR THE PREPARATION OF CEFDITOREN USING THE THIOESTER OF THIAZOLYLACETIC ACID

Field of Invention

The present invention relates to a process for the preparation of Cefditoren of formula (I), the pivaloyloxy methyl ester (Cefditoren pivoxil) of which is well known to be used as an antibiotic agent.



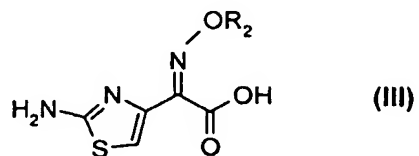
The present invention more particularly relates to a process for the preparation of Cefditoren using the thioester derivatives of formula (II)



wherein, R₁ represents C₁ - C₄ alkyl or phenyl. The thioester derivatives of formula (II) have been disclosed and claimed in the US Patent No. 6,388,070.

Background of the Invention

Acid chlorides, anhydrides, esters, amide etc. are reported in the chemical literature for activation of carboxylic acid of formula (III).



wherein, R₂ represents H, trityl, CH₃, CR_aR_bCOOR_c, (in which R_a and R_b independently of one another represent hydrogen or methyl and R_c represents H or C₁-C₇ alkyl).

In these, activation in the form of acid chloride required protection and deprotection of NH_2 group.

Activation of acid (III) is reported by $\text{SO}_2\text{Cl}_2/\text{DMF}$ in US patent 5,856,502 and SOCl_2/DMF in US patent 5,037,988. These processes suffer the limitation of using
5 harmful and pungent smelling chemicals like SOCl_2 , SO_2Cl_2 along with solvents like benzene, toluene, etc. and stringent conditions required for carrying out the reactions at commercial scale.

In US patent Nos. 4,576,749 and 4,548,748 the acid of formula (III) has also been activated by reacting with 1-hydroxybenzotriazole (HOBt) or 2-mercaptobenzothiazole
10 (MBT) in the presence of dicyclohexylcarbodiimide (DCC) to produce reactive ester of the acid (III) which then reacted to cephem moiety to prepare cephem antibiotics, but the processes are time consuming and with low yields, hence not suitable.

US patent No. 4,767,52 discloses a process for the production of cepheims by acylating 7-amino-3-cephem-4-carboxylic acid with 2-mercaptobenzothiazolyl-(Z)-2-(2-
15 aminothiazol-4-yl)-2-methoxyiminoacetate (MAEM). Similarly, US Pat.No.5,026,843 (1991) discloses a process for preparing ceftriaxone disodium hemiheptahydrate by acylation of ACT by using MAEM as acylating agents in good yield and quality. Thus, MAEM has become the standard acylating agent for the preparation of cephalosporins having an oximino group and a 2-aminothiazolyl group in 7-position of cephem
20 compounds.

However, the synthesis of MAEM from acid (III) and 2,2'-dithio-bis-benzothiazole involves use of costly condensing agent triphenylphosphine (TPP). Moreover, during condensation of MAEM with 7-amino-3-cephem-4-carboxylic acid compound (IV), a toxic compound MBT is also produced as a byproduct, see e.g., Chemical Abstracts, 111,
25 19243p (1989) which is difficult to remove completely.

Thus, it is evident that the procedures described in the prior art for preparation of these antibiotics are complex, involving protection, deprotection and are associated with toxic byproduct generation. Hence, there is a need to develop new acylating agents which are capable of transferring the 2-aminothiazolyl moiety to cephem compounds of formula (IV) in good yield but without producing this toxic byproduct. On the similar lines, a new thioester was reported by D.G.Walker, Tet. Lett. 1990, 31,6481 to acylate the cephem moiety to get cefepime sulfate but yields obtained by using this thioester were in the range of 54-73% which cannot be considered as good yield to operate the process at commercial scale. The use of this thioester was also reported in the Tet. Lett. 1990, 31, 6481 only for cefepime and not for other cephalosporins. This thioester was exploited in US patent No. 5,869,649 for making three other important cephalosporin antibiotics.

Objectives of the Invention

The primary objective of the invention is to provide a process for the preparation of Cefditoren of formula (I), using the thioester derivatives of thiazolyl acetic acid of the general formula (II), which is a better reactive derivative than the other reactive derivatives.

Another objective of the present invention is to provide a process for the preparation of Cefditoren of formula (I), which is simple, high yielding and cost effective.

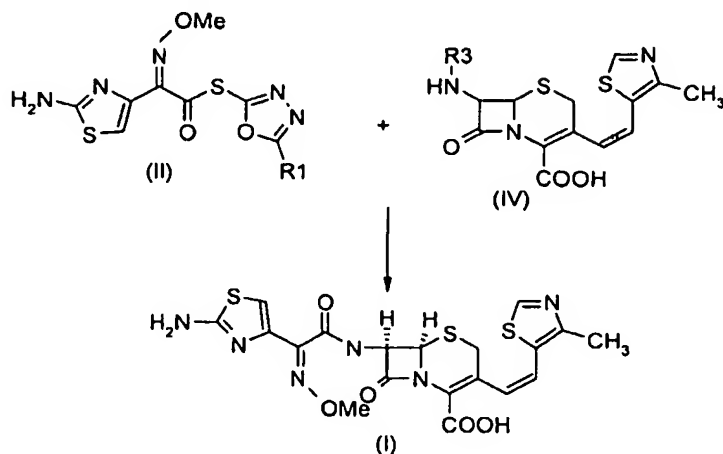
Still another objective of the present invention is to produce Cefditoren of formula (I), which is highly pure and free from toxic by-products.

Summary of the Invention

Accordingly, the present invention provides a process for the preparation of Cefditoren of formula (I), which comprises acylating 7-amino-cephem carboxylic acid of the general formula (IV) where R₃ is hydrogen or trimethylsilyl group with thioester derivative of formula (II) where R₁ represents C₁ - C₄ alkyl or phenyl in an organic solvent

and in the presence of an organic base at a temperature in the range of -10°C to 30°C .

The process is shown in Scheme-1 herebelow:



Scheme-1

Wherein, R_1 and R_3 are as defined above.

Detailed Description of the Invention

The condensation of cephem compound of formula (IV) with thioester of formula (II) is performed by two different methodologies (a) by acylating the compound of formula (IV) (when R_3 is H) with formula (II) in an aqueous organic solvent; (b) by acylating the compound of formula (IV) (when R_3 is silyl) with formula (II) in an aprotic organic solvent. Both the approaches are comparable and afforded excellent yields and purities of cephalosporin antibiotics of formula (I).

Acylation of compounds of formula (IV) (when R_3 is H) is performed in the presence of a water miscible solvent selected from tetrahydrofuran (THF), acetonitrile, acetone, dioxane, N,N-dimethylformamide etc., but the preferable solvent is THF or acetonitrile.

Acylation of compound of formula (IV) (when R_3 is silyl) was carried out in an aprotic organic solvent selected from halogenated hydrocarbons, toluene, alkyl ethers etc., but preferable solvent is dichloromethane. Suitable silylating agent used for the reaction is

selected from hexamethyldisilazane, bis(trimethyl)silylacetamide or trimethylsilyl chloride.

In another embodiment of the present invention, the organic base may be selected from triethylamine, diethylamine, tributylamine, N-alkylpyridine, N-alkylanilines, 1,8-diazabicyclo[5.4.2]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, N-methylmorpholine, 1,4-diazabicyclo[2.2.2]octane, 4-dimethylamino pyridine or mixtures thereof.

In another embodiment of the present invention, the Cefditoren of formula (I) obtained is a syn-isomer.

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In yet another embodiment of the present invention, the Cefditoren of the formula is Z-isomer.

The present invention provides a method by which cephalosporin antibiotics are obtained in high purity (95-99%) and excellent yield (79-95%) without the necessity for protecting the amino group of the acylating agents and the production of toxic byproduct namely 2-mercaptobenzothiazole is avoided.

Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure. However, since the major characteristic feature of the present invention resides in the use of novel reactive thioester derivatives of thiazolyl acetic acid of the general formula (II) in preparing the Cefditoren of formula (I) the technical scope of the present invention should not be limited to the following examples.

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The following examples are provided to illustrate but not to limit the claimed invention.

EXAMPLES

Example - I

Synthesis of 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (II):

5 (Z)-(2-aminothiazol-4-yl)methoxyimino acetic acid (20.1 g), triethylamine (22.2 g) were suspended in dry dichloromethane (150 ml), and then bis-(2-oxo-oxazolidinyl) phosphinic chloride (25.4 g) was added in one lot at 0-5 °C and stirred for 1 hr. The 2-mercapto-5-phenyl-1,3,4-oxadiazole (21.3 g) was added at 0-5°C. The reaction mixture was stirred for 3-4 hours. After the reaction was complete, distilled water (100 ml) was added to the
10 reaction solution and the mixture was stirred for 10 min. The organic layer was separated and washed successively with 2% aq. solution bicarbonate solution (100 x 2 ml) and saturated saline (100 ml), dried over sodium sulphate, filtered and then concentrated under reduced pressure. To the residue, IPE (300 ml) was added and solid was filtered, washed with IPE (100 ml). Dried to obtain 30.6 g (yield 85 %) of the title compound as light
15 yellow solid.

Melting point : 109 – 110 °C

¹H-NMR (DMSO-d₆) : δ 3.90 (3H,s,N-OCH₃), 7.11(1H,s, thiazole ring proton),
7.29(2H,bs,NH₂), 7.6-7.9(5H, m, - C₆H₅)

20 ¹³C-NMR (Acctone-d₆): δ 63.16, 108.7, 122.1, 129.7, 132.6, 133.7, 141.6, 146.75, 159.3, 159.6, 169.7, 173.1.

Example - II

25 **3-[(Z)-2-(4-methyl-5-thiazolyl)vinyl]-7-[(Z)-(2-aminothiazolyl-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylic acid (Cefditoren acid):**

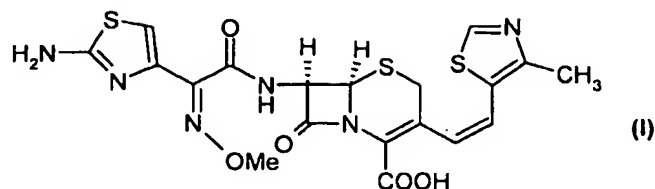
A mixture of THF (250ml) and water (150ml) was stirred under inert atmosphere. At 0°C – 1°C, 7-amino-3-[(Z)-2-(4-methyl-5-thiazolyl)vinyl]-3-cephem-4-carboxylic acid (25.0 g)

and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (33.3 g) obtained in Example I were added. Triethylamine (10.5 g) was slowly added to reaction by maintaining the pH between 7.5 to 8.5. The reaction was monitored by HPLC. After 4-5 hrs., the reaction mixture was extracted by methylene chloride. The aqueous layer is subjected for charcoal (0.125 g) treatment. Ethylacetate was added to the filtrate and the solution was acidified with dil. HCl at 10°C to pH 3.0. The solid separated was filtered, washed with water and ethylacetate and then dried under vacuum at 40-45°C to get Cefditoren acid, 35.0 g (yield 90 %).

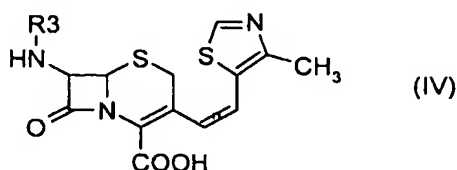
HPLC (purity)= 96 - 98%

CLAIMS

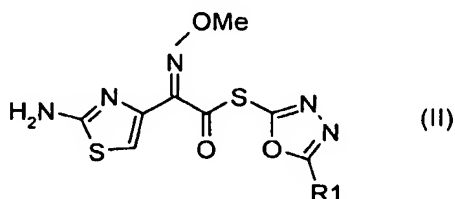
1. A process for the preparation of Cefditoren of formula (I)



- 5 which comprises acylating a compound of formula (IV)



wherein, R₃ is hydrogen or trimethylsilyl, with a compound of formula (II)



- 10 wherein R₁ represents C₁ - C₄ alkyl or phenyl, in the presence of an organic solvent, an organic base and a silylating agent at a temperature in the range of -10 °C to 30 °C.

2. The process of claim 1, wherein the compound of formula (I) is a syn isomer.
- 15 3. The process of claim 1, wherein R₃ is H, the acylation is done in the presence of a mixture of water and an organic solvent selected from the group consisting of tetrahydrofuran, acetonitrile, acetone, dioxane, N,N-dimethylformamide, or mixtures thereof.
4. The process of claim 1, wherein when R₃ is trimethylsilyl, the acylation is carried
- 20 out in an aprotic organic solvent selected from halogenated hydrocarbon, toluene or alkyl ether preferably in alkyl ether.

5. The process of claim 1, wherein said acylation is performed in the presence of an organic base selected from triethylamine, diethyleamine, tributylamine, N-alkylpyridine, N-alkylanilines, 1,8-diazabicyclo[5.4.2]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 4-dimethylaminopyridine, or mixtures thereof.
6. The process of claim 1, wherein the silylating agent used is trimethylsilyl halide.
7. The process of claim 6, wherein the trimethylsilyl halide used is trimethyl silyl chloride.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/01781

CLASSIFICATION OF SUBJECT MATTER

IPC⁷: C07D 501/04, 501/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁷: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT Patent documents

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI Database, Derwent Publications LTD., REGISTRY, CAPLUS and CASREACT
Databases, STN International, EPO PAJ Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6388070 B1 (P. B. DESPHANDE et al.) 14 May 2002 (14.05.02) <i>the whole document, esp. claims, examples, column 5 - line 26.</i>	1-7
A	US 4767852 A (G. ASCHER) 30 August 1988 (30.08.88) <i>the whole document.</i>	1-7
A	EP 0806424 A1 (RANBAXY LABORATORIES, LTD.) 12 November 1997 (12.11.97) <i>the whole document.</i>	1-7
A	US 5869649 A (J. M. KHANNA et al.) 9 February 1999 (09.02.99) <i>the whole document.</i>	1-7

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

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Name and mailing address of the ISA/AT

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Telephone No. 1/53424/341

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 02/01781-0

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
EP	A1	6424	09-01-1980	DE	A1	2817491	31-10-1979
US	A	4767852	30-08-1988	AT	E	9352	15-09-1984
				AU	A1	68859/81	01-10-1981
				AU	B1	550168	06-03-1986
				CA	A1	1172627	14-08-1984
				CA	A2	1191853	13-08-1985
				CY	A	1365	07-08-1987
				DE	C0	3165922	18-10-1984
				DK	A	1387/81	29-09-1981
				DK	A	1572/91	06-09-1991
				DK	A0	1572/91	06-09-1991
				DK	B	163243	10-02-1992
				DK	C	163243	29-06-1992
				DK	B1	167680	06-12-1993
				EP	A2	37380	07-10-1981
				EP	A3	37380	02-12-1981
				EP	B1	37380	12-09-1984
				ES	A1	500792	01-06-1982
				ES	A5	500792	30-06-1982
				ES	A1	8205228	16-09-1982
				ES	A1	509957	16-06-1983
				ES	A5	509957	12-07-1983
				ES	A1	8307007	01-10-1983
				FI	A	810948	29-09-1981
				FI	A	864119	13-10-1986
				FI	A0	864119	13-10-1986
				FI	B	74019	31-08-1987
				FI	C	74019	10-12-1987
				HK	A	806/87	06-11-1987
				HR	A1	940988	29-02-1996
				HR	B1	940988	29-02-1996
				IE	B	51831	15-04-1987
				IL	A0	62506	20-05-1981
				IL	A1	62506	31-01-1986
				JP	A2	56152488	26-11-1981
				JP	A2	2000177	05-01-1990
				JP	B4	3013237	22-02-1991
				JP	B4	5067632	27-09-1993
				KE	A	3724	29-05-1987
				NZ	A	196642	31-07-1984
				NZ	A	206261	31-07-1984
				PH	A	17071	24-05-1984
				PT	A	72736	01-04-1981
				PT	B	72736	13-07-1982
				SG	A	352/87	20-05-1988
				SI	A8	8110798	31-12-1994
				SI	A8	8311227	31-12-1994
				US	A	5003073	26-03-1991
				YU	A	798/81	31-12-1983
				YU	A	1227/83	31-12-1986
				YU	B	43764	31-12-1989
				ZA	A	8102083	24-11-1982
				YU	B	43179	30-04-1989
				HR	B1	940989	30-04-1996
US	A	5869649	09-02-1999	NZ	A	314377	19-12-1997
				ZA	A	9702080	17-09-1997
				AU	A1	16261/97	25-09-1997
				AU	B2	690482	23-04-1998
				CN	A	1167112	10-12-1997
				EP	A1	806424	12-11-1997
				TW	B	394775	21-06-2000
US	BA	6388070	14-05-2002	WO	A1	02053563	11-07-2002